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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,623	06/20/2003	Uri H. Saragovi	351325-0102 OGIL-002 US	7195

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
03/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/600,623	SARAGOVI ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31-35 and 39* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 11/19/2007 in response to the previous Non-Final Office Action (9/01/2006) is acknowledged and has been entered.

Claims 1-29, 31-35 and 39 are pending.

Claims 1-29 and 31-34 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 35 and 39 are currently under consideration.

Rejections Withdrawn:

The rejection of Claim 39 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of Applicants arguments. In particular, Applicants showing that α-IR3 and MC192 are both commercially available through Calbiochem(R) catalogue and submission on record that the monoclonal antibody 5C3 is known in the art and described in US Patent No. 6,610,500 as having the amino acid sequence described in Example III column 16, line 50 to column 17, lines 35 of US Patent No. 6,610,500.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saragovi et al. (WO 97/21732, 1997, IDS) in view of Webb et al. (US 6,652,864, filed on 12/21/19980 and Shin et al. (Cancer Immunol. Immunother. 1994; 38: 92-98).

Saragovi et al. teach a method of treating a neoplastic tumor which expresses TrKA receptors in a patient comprising administering an effective amount of an antibody or functional fragment thereof (page 4, lines 8-14). With regards to the antibody, the WO document teaches that the antibody includes, but is not limited to, monoclonal antibody 5C3 (page 7, lines 6+). Moreover, the WO document teaches that the method of treating a tumor further comprises coupling a cytotoxic agent to the antibody and administering to said patient the coupled antibody (page 5, lines 8-14).

Saragovi et al. do not explicitly teach that the coupled antibody has the formula W-Z-X, wherein X is a chemotherapeutic agent selected from the group consisting of doxorubicin and paclitaxel, W is the monoclonal antibody, 5C3, and z is a breakable linker which covalently links W and X.

Webb et al. teach a compound having the formula B-L-M, wherein B is a binding agent capable of selectively binding to a nerve cell surface receptor, M is a moiety and L is a linker which couples L to M (column 2, lines 3-14). In particular, the patent teaches that the binding agents are antibodies including, but not limited to, monoclonal antibodies 5C3 and anti-human p75 monoclonal antibody MC192 (column 2, lines 56-60). Moreover, the patent teaches that linker is a cleavable linker which enables the moiety M linked to the binding agent B to be released from the compound once absorbed by the nerve cell (column 3, liens 16-20).

Shih et al. teach that the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein the maximum tolerated dose that a patient can receive is often lower than is necessary for tumor destruction (page 92, 2nd column, 1st paragraph). As such, Shin et al. teach a doxorubicin immunoconjugate, e.g., doxorubicin conjugated to an anti-CEA antibody, which exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system that has been resistant to most of the available chemotherapeutic agents, and revealed minimal host toxicity when compared to an equivalent dose of the free drug, e.g., unconjugated doxorubicin (page 92, 2nd column, 2nd paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al. One would have been motivated to do so because Webb et al. teach that the incorporation of a cleavable linker between the binding agent and moiety enables the moiety to be released once absorbed by the nerve cell, e.g., TrKA receptor. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include a cleavable linker between the antibody and cytotoxic antibody in view of the teachings of Webb et al., one would achieve a method of treating a tumor, wherein the cytotoxic agent is released from 5C3 within the tumor.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al.. One would have been motivated to do so because Shih et al. teach the major limitation of conventional cancer chemotherapy is the non-selectivity of this treatment, wherein a doxorubicin immunoconjugate exhibited substantially increased tumorcidal effects over those of the unconjugated doxorubicin in the tumor system. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al., one would achieve a method of reducing the major limitation of non-selectivity of doxorubicin treatment.

In response to this rejection, Applicants contend that none of the cited references teach or suggest, alone or in combination, the instantly claimed invention of a method of treating a patient with a tumor via bypassing the p-glycoprotein pump or even bypassing multidrug resistance. For example, Applicants assert that while Saragovi et al. teach treating tumors with 5C3, including treating a tumor by coupling a cytotoxic agent to the antibody, Saragovi et al do not teach a breakable linker between the cytotoxic agent and the antibody, or treatment of tumor cells by bypassing the p-glycoprotein pump. Similarly, Applicants assert that while Webb et al. teach a binding agent that binds selectively to a neurotrophin receptor expressed in nerve cells (including 5C3 and MC192), a cleavable linker and a non-cytotoxic, therapeutic agent and Shih et al. teach an immunoconjugate of an anti-CEA antibody to doxorubicin for treating tumors, none of the

references teach or suggest, alone or in combination, compounds to bypass the p-glycoprotein pump. In the instant case, Applicants assert that the binding of the compounds of the invention bypass the p-glycoprotein pump after binding to tumor cells, and can treat a patient with a tumor by bypassing the p-glycoprotein pump as claimed herein, was unexpected. Thus, Applicants assert that a person of skill in the art would not have a reasonable expectation that the conjugates could be used to bypass the p-glycoprotein pump in treatment of tumors.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner acknowledges that Applicants have amended the instant claims to recite the limitation of bypassing the p-glycoprotein pump and does not dispute Applicants assertions that the cited combination alone or in combination, does not teach or suggest that the compounds can bypass the p-glycoprotein pump. However, the Examiner recognizes that the newly added limitation appears to be the mechanism of action by which the tumor are treated, see for example, Applicants statement that the binding of the compounds of the invention bypass the p-glycoprotein pump after binding to tumor cells. Hence, even though the claims are drawn to a mechanism by which the compounds treat the tumors, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. In the instant case, the Examiner recognizes that the cited combination teaches the same or nearly the same method of administering the claimed conjugate to the same patient population for the treatment of cancer. Secondly, Applicant has argued and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA

1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, both Saragovi et al. and Webb et al. represent analogous teachings of using Trk antibody conjugates for the treatment of a disease in a patient. Whereas, Shih et al. represents the knowledge one of skill in the art would possess at the time the invention was made with regards to immunoconjugates. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the coupled antibody as taught by Saragovi et al. to include doxorubicin as the cytotoxic moiety in view of the teachings of Shih et al., one would achieve a method of reducing the major limitation of non-selectivity of doxorubicin treatment. Lastly, regarding Applicants assertions of unexpected results, the Examiner acknowledges Applicants assertions that bypassing of the p-glycoprotein pump was unexpected. However, the Examiner recognizes that objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results. Thus, Applicants assertions of unexpected results in a moot point absent any factual support.

Therefore, NO claim is allowed

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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